IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s): Irvin, et al.
Appl. No.: 09/865,159
Filed: May 24, 2001
Title: PSEUDOMONAS TREATMENT COMPOSITION AND METHOD
Art Unit: 1645
Examiner: J. Graser
Docket No.: 113190-064

Commissioner for Patents
Washington, DC 20231

AFFIDAVIT OF ANDREW J. MALCOLM UNDER 37 C.F.R. § 1.132

I, Andrew J. Malcolm, hereby state as follows:

1. I am employed by Cytovax Biotechnologies Inc. as Vice President of Research and Development. My educational background is as follows: B.Sc.(Biology Honors) Bishop's University, Lennoxville,Quebec (1975); M.Sc. (Immunology) University of Manitoba, Winnipeg, Manitoba (1978); and Ph.D. (Immunology/Microbiology) University of British Columbia, Vancouver, British Columbia (1983). My employment background is as follows:

(1975-78) **M.Sc. student**, Allergy research, Dept. of Immunology, University of Manitoba, Winnipeg, Manitoba

(1978-79) **Medical Researcher**, Bladder and kidney cancer research, Urology Division, Department of Surgery, Institute of Biology, Health Sciences Centre, Winnipeg, Manitoba

(1979-83) **Ph.D. student**, Human myelogenous leukemia research, Dept. of Microbiology, University of British Columbia, Vancouver, British Columbia

(1983-84) **Industrial Postdoctoral Fellow**, Human leukemia research, Quadra Logic Technologies Inc., Vancouver, British Columbia

(1984-85) **Postdoctoral Fellow**, Human bone marrow transplantation research, Fred Hutchinson Cancer Research Center, Seattle, Washington, U.S.A.

(1986) **Research Associate**, Osteoarthritis research, Department of Medicine, University of British Columbia, Vancouver, British Columbia

(1987-90) **Research Associate**, Regulatory peptide research, Department of Physiology, University of British Columbia, Vancouver, British Columbia

(1990-91) **Group Leader**, Vaccine Development and Transplantation Immunology, Chembiomed Ltd., Edmonton, Alberta

(1991-1997) **Group Leader/ Research Scientist**, Immunology Research and Vaccine Development, Biotechnology Department, Alberta Research Council, Edmonton, Alberta

(1993-pres) **Adjunct Profess r,** Department of Laboratory Medicine and Pathology, Faculty of Medicine, University of Alberta, Edmonton, Alberta
(1997-2000) **Vice President, Immunodiagnostics,** Is technika Inc., Edmonton, Alberta
(1998-pres) **Adjunct Professor,** Department of Surgery, Faculty of Medicine, University of Alberta, Edmonton, Alberta
(2000-2002) **Vice President of Research,** Cytovax Biotechnologies Inc., Edmonton, Alberta
(2002-pres) **Vice President of Research and Development,** Cytovax Biotechnologies Inc., Edmonton, Alberta. Attached hereto as Exhibit A is a copy of my Curriculum Vitae.

2. I am familiar with the above-identified patent application and have read the sole pending claim, namely Claim 20 provided as follows:

Claim 20. A method of treating or preventing infection by *Pseudomonas aeruginosa* comprising administering a pharmaceutically acceptable amount of an isolated pilin peptide having the amino acid sequence set forth in SEQ ID Nos. 4, 6, 8, or 10.

3. I have also reviewed the Office Action pending against the above-identified patent application dated February 11, 2002. A copy of the Office Action is attached hereto as Exhibit B.

4. It is my understanding that the Patent Office has rejected Claim 20 under 35 U.S.C. § 112, first paragraph. As one skilled in the art, I do not believe the rejection of Claim 20 is proper.

5. Based on my review and understanding of the claimed invention as disclosed and supported in the specification, I have conducted an experiment to demonstrate that truncated recombinant pilin from various clinically relevant strains of *Pseudomonas aeruginosa* (PAK, PAO, K122-4, KB7 or P1) could act as a therapeutic to block bacterial adhesion to mucosal cells.

6. The test recombinant pilin were engineered based on my knowledge as one skilled in the art and in view of what was disclosed in the Specification of the present application. For example, pages 9-11 of the Specification describe how recombinant pilin can be made.

7. The test recombinant pilin included the amino acid sequence set forth in SEQ ID Nos. 4, 6, 8, or 10 as required by Claim 20. The PAK recombinant pili (PAK rec pili) included SEQ ID No. 4; the PAO recombinant pili (PAO rec pili) included SEQ ID No. 6; the P1

recombinant pili (P1 rec pili) included SEQ ID No. 8; and the KB7 recombinant pili (KB7 rec pili) included SEQ ID No. 10. The K122-4 recombinant pili (K122-4 rec pili) included SEQ ID No. 2.

8. Based on my knowledge as one skilled in the art and in view of what was disclosed in the Specification of the present application, such as Example 5 on pages 13 and 14, the recombinant pilin were tested as follows. A 200 μL volume containing 200 μg of recombinant pili (PAK, or PAO, or K122-4, or KB7 or P1) was intraperitoneally (i.p.) injected into groups of 10 A.BY/SnJ mice (18 – 20 grams, 10 weeks). A BSA negative and a non-injected control group was also included. After one hour, a lethal dose of *P. aeruginosa* PAK wildtype, was administered intraperitoneally to these mice. The experimental protocol is illustrated below:

Pilin Adhesion Inhibition Experiment

Groups (10 A.BY mice/group)

1. i.p. Injected 200 µL 200 µg/mouse PAK rec pili 1 hour pre challenge*
2. i.p. Injected 200 µL 200 µg/mouse PAO rec pili 1 hour pre challenge*
3. i.p. Injected 200 µL 200 µg/mouse K122-4 rec pili 1 hour pre challenge*
4. i.p. Injected 200 µL 200 µg/mouse P1 rec pili 1 hour pre challgenge*
5. i.p. Injected 200 µL 200 µg/mouse KB7 rec pili 1 hour pre challenge*
6. i.p. Injected 200 µL 200 µg/mouse BSA 1 hour pre challenge*
7. Non Injected control*

*Groups 1 – 7 were i.p. challenged with *P. aeruginosa* strain PAK (0.77×10^6 cfu/mouse) bacteria.

9. Mice were then monitored for survival over a 48 hour period. As demonstrated in the survival graph attached hereto as Exhibit C, mice administered various truncated pilin (PAK, or PAO, or K122-4, or KB7 or P1) showed significant protection to bacterial challenge, non-injected or BSA control group mice showed little survival or little protection to bacterial

challenge. I believe this result indicates that the truncated pilin from PAK, or PAO, or K122-4, or KB7 or P1 bind to a common mucosal cell receptor. This binding blocks the adherence of *P. aeruginosa* bacteria and hence, in my opinion, inhibits the initiation of the infection process.

10. The percent survival of the various mouse groups in this pilin adhesion inhibition experiment is shown in the table attached hereto as Exhibit D. The mean survival times of mice treated with PAK or PAO or K122-4 or KB7 or P1 truncated recombinant pilin were significantly higher (38 – 42 hours) than the mean survival times of non-injected or BSA control mice (25 – 28 hours). I believe that the results of this experiment demonstrate that PAK, PAO, K122-4, P1 or KB7 recombinant pilin can block adherence of *P. aeruginosa* to mucosal cells thereby preventing bacterial colonization and the infection process.

11. Based on my review of the present application including pending Claim 20 and the written description and my knowledge as a skilled artisan, I have conducted experiments that, in my opinion, demonstrate recombinant pilin can be used as a therapy or a combination therapy for the treatment of *Pseudomonas* bacterial infections as required by the claimed invention. Therefore, I believe that the subject matter as required by Claim 20 is clearly enabling such that one skilled in the art could make or use same without having to undergo undue experimentation.

12. I hereby declare that all statements made herein of my own knowledge are true and that all statements made upon information and belief are believed to be true; and further that these statements and the like so made are punishable by fine or imprisonment, or both, under §1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of any patent that may issue from this application.

FURTHER AFFIANT SAYETH NOT:

Andrew J. Malcolm

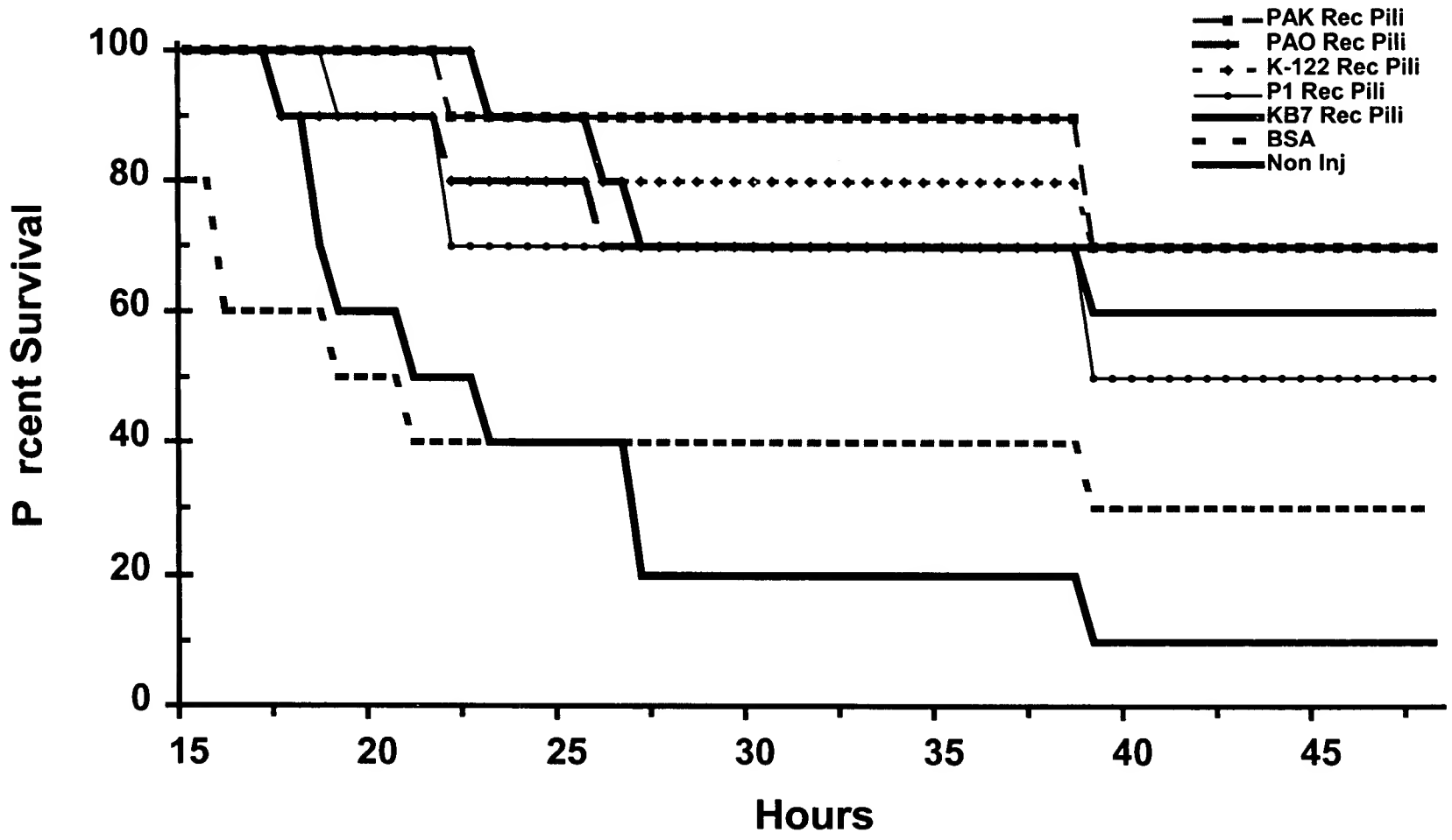
Andrew J. Malcolm, Ph.D.

August 9, 2002

Date

Survival Curves in Pilin Adhesion Inhibition Experiment

Lethal PAK Bacteria Challenge(0.77 X 106 cfu/mouse)



Percent Survival in Pilin Adhesion Inhibition Experiment

PAK Challenge (0.77 x 10^6 cfu/Mouse)		
Groups	**Percent Survival**	**Mean Survival Time (hrs.)**
PAK REC PILI	**70%**	**43.6**
PAO REC PILI	**70%**	**40.1**
K122-4 REC PILI	**70%**	**42.4**
PI REC PILI	**50%**	**38.1**
KB7 REC PILI	**60%**	**40.3**
BSA	**30%**	**28.5**
NON INJECTED	**10%**	**25.8**

CURRICULUM VITAE

Andrew J. Malcolm
Vice President of Research and Development
Cytovax Biotechnologies Inc.
8223 Roper Road
Edmonton, Alberta, T6E 6S4

EDUCATION

1975	B.Sc. (Biology Honors) Bishop's University, Lennoxville,Quebec
1978	M.Sc. (Immunology) University of Manitoba, Winnipeg, Manitoba
1983	Ph.D. (Immunology/Microbiology) University of British Columbia, Vancouver, British Columbia

AREAS OF RELEVANT EXPERIENCE

- research background in Cell Biology/Microbiology/Immunology.
- research and lab management positions in academic and industrial setting - 20 years post Ph.D.
- experience in basic and clinically related projects in transplantation, hematology, arthritis, allergy, oncology and tumor biology.
- development projects in monoclonal antibody production, vaccine technology, immunosuppressant and drug efficacy / toxicity testing, therapeutic drug monitoring, identifying and isolating antigens, isolating cell receptors and studying immunostimulators and immune response modifers.
- managed monoclonal antibody production and development labs and have extensive experience developing monoclonal antibody based immunoassays.
- developed automated diagnostic assays.
- established animal models for pre-clinical testing of new therapeutics and modalities.
- written successful IND submissions, grant proposals and industrial contracts.
- inventor of issued patents and published in scientific journals
- managed patent portfolios and prosecution.
- prepared business development plans and negotiated commercialization contracts

RELEVANT TECHNIQUES

Tissue culture and large scale growth (bacterial and mammalian), monoclonal and polyclonal antibody production and purification, development of immunoassays and diagnostic kits (ELISA, RIA, Immunoblot, automated assay systems), isolation and characterization of tumor-associated, adhesion and other antigens (protein / carbohydrate / lipoprotein), column chromatography, affinity columns, electrophoresis and blot analysis, growth of malignant and normal hematopoietic cells (CFU-C), cytotoxicity assay (NK, LAK, CTL, MLR), immunocytochemistry and flow cytometry analysis techniques, polysaccharide

extraction, oligosaccharide preparation by enzymatic cleavage or acid hydrolysis, chemical conjugation techniques, opsonization, bactericidal assays and vaccine development. Establishing experimental animal models and *in vitro* culture experiments with human lymphocytes, mammalian and bacterial cells.

PROFESSIONAL EMPLOYMENT HISTORY

(1975-78) **M.Sc. student**, Allergy research, Dept. of Immunology, University of Manitoba, Winnipeg, Manitoba

(1978-79) **Medical Researcher**, Bladder and kidney cancer research, Urology Division, Department of Surgery, Institute of Biology, Health Sciences Centre, Winnipeg, Manitoba

(1979-83) **Ph.D. student**, Human myelogenous leukemia research, Dept. of Microbiology, University of British Columbia, Vancouver, British Columbia

(1983-84) **Industrial Postdoctoral Fellow**, Human leukemia research, Quadra Logic Technologies Inc., Vancouver, British Columbia

(1984-85) **Postdoctoral Fellow**, Human bone marrow transplantation research, Fred Hutchinson Cancer Research Center, Seattle, Washington, U.S.A.

(1986) **Research Associate**, Osteoarthritis research, Department of Medicine, University of British Columbia, Vancouver, British Columbia

(1987-90) **Research Associate**, Regulatory peptide research, Department of Physiology, University of British Columbia, Vancouver, British Columbia

(1990-91) **Group Leader**, Vaccine Development and Transplantation Immunology, Chembiomed Ltd., Edmonton, Alberta

(1991-1997) **Group Leader/ Research Scientist**, Immunology Research and Vaccine Development, Biotechnology Department, Alberta Research Council, Edmonton, Alberta

(1993-pres) **Adjunct Professor**, Department of Laboratory Medicine and Pathology, Faculty of Medicine, University of Alberta, Edmonton, Alberta

(1997-2000) **Vice President,Immunodiagnostics**, Isotechnika Inc., Edmonton, Alberta

(1998-pres) **Adjunct Professor**, Department of Surgery, Faculty of Medicine, University of Alberta, Edmonton, Alberta

(2000-2002) **Vice President of Research**, Cytovax Biotechnologies Inc., Edmonton, Alberta

(2002-pres) **Vice President of Research and Development**, Cytovax Biotechnologies Inc., Edmonton, Alberta

TEACHING, CONSULTING AND SUPERVISORY RESPONSIBILITIES:

(1979-82) Teaching Assistant, Department of Microbiology, University of British Columbia, Vancouver, B.C.

(1983-84) Supervisor of tissue culture facility and technical staff, Quadra Logic Technologies, Inc., Vancouver, B.C.

(1986) Supervisor of technical staff, Department of Medicine, University of British Columbia, Vancouver, B.C.

(1987-90) Supervisor of core monoclonal laboratory & technical staff, Dept. of Physiology, University of British Columbia, Vancouver, B.C.

(1988-89) Lecturer, University of British Columbia course in Animal Cell Culture, Vancouver, B.C.

(1988-89) Supervisor of Biology 448 (Directed Studies), Department of Biology, University of British Columbia, Vancouver, B.C.

(1988 & 89) Supervisor of summer student research projects, University of British Columbia, Vancouver, B.C.

(1990-1991) Supervisor of technical staff, Vaccine Development and Transplantation Immunology, Chembiomed Ltd., Edmonton, Alberta

(1991-1997) Supervisor of technical staff, Immunology Research and Vaccine Development, Alberta Research Council, Edmonton, Alberta

(1993-1997) Supervisor of technical staff, Department of Laboratory Medicine and Pathology, University of Alberta, Edmonton, Alberta

(1993/94/95) Supervisor of NSERC summer student research projects, Alberta Research Council, Edmonton, Alberta

(1995-pres) Graduate student project supervision and committees - Department of Laboratory Medicine and Pathology, Department of Surgery, University of Alberta, Edmonton, Alberta

(1997-2000) Supervisor of technical staff, Immunodiagnostics Department, Isotechnika Inc., Edmonton, Alberta

(1998-2000) Consultant for Biotechnology Department, Alberta Research Council, Edmonton, Alberta

(2000-pres) Supervisor of research staff, Cytovax Biotechnologies Inc., Edmonton, Alberta

SOCIETY MEMBERSHIPS:

Canadian Society for Immunology
International Society for Neuroimmunomodulation
International Society for Vaccines
The New York Academy of Sciences

UNDERGRADUATE AND GRADUATE STUDENT AWARDS:

1974-75	Academic Affairs Award
1975-78	MRC Studentship - MRC Group in Allergy Research
1979-83	British Columbia Health Care Research Studentship

POSTDOCTORAL AWARDS:

1983-84	Science Council of British Columbia Industrial Postdoctoral Fellowship Award.
1984-85	Pacific Northwest Research Foundation Postdoctoral Fellowship Award
1986	CIBA-Geigy Canada Ltd. Research Associate Award

RESEARCH GRANTS/CORPORATE SPONSORS:

1986	CIBA-Geigy Canada Ltd. - Osteoarthritis Research
1986	Heighway Foundation Equipment Grant - Osteoarthritis Research
1987-90	Faculty member with MRC Funded Regulatory Peptide Group, Physiology Department, UBC
1990-92	Canadian Bacterial Diseases Network - Vaccine Research
1992-1997	Biotransplant Incorporated - Xenotransplant Research
1993-96	SmithKline Beecham Biologicals-Vaccine Research
1994-1997	CIBA-Corning Diagnostics Corporation - Monoclonal Antibody Diagnostics
1996-1997	Synsorb Biotech Inc. - Immunoassay Development
1997-pres	Alberta Research Council- Xenotransplant Research
1997-2000	National Research Council – Anti-Cancer Drug Research
1997-2000	Boehringer Mannheim Corporation / Microgenics – Therapeutic Drug Monitoring
1998-2000	Dade Behring Inc. – Therapeutic Drug Monitoring
1998-2000	Abbott Laboratories – Monoclonal Antibody Diagnostics
1999-2000	Diasorin Inc.- Diagnostics Development

PRESENTATIONS

1. N.A.T.O. Advanced Study of Institute on "Molecular and Cellular Aspects of Allergy". Falcon Lake, Manitoba, Canada, June 1976. (Poster)

2. Canadian Federation of Biological Sciences Meeting, London, Ontario, Canada, June 1978. (Oral presentation)

3. Pacific Northwest Immunology Society Meeting, Mt. Hood, Oregon, U.S.A., April 1980. (Poster)

4. Canadian Federation of Biological Sciences Meeting, Montreal, Quebec, Canada, June 1981. (Poster)

5. Hematopoietic Stem Cell Conference, Honey Harbour, Ontario, Canada, September 1981. (Poster)

6. Invited speaker at Pacific Northwest Immunology Society Meeting, Banff, Alberta, Canada, June 1982.

7. U.C.L.A. Symposium on Bone Marrow Transplantation, Salt Lake City, Utah, U.S.A, February 1983. (Poster)

8. Invited speaker at the Fred Hutchinson Cancer Research Centre, Seattle, WA., U.S.A., October 1983. Sponsor: Dept. of Pediatric Oncology, F.H.C.R.C.

9. First International Terry Fox Conference, Vancouver, B.C., Canada, August 1984. (Poster)

10. Invited speaker at M.D. Anderson School of Medicine, The University of Texas System Cancer Centre, Houston, Texas, U.S.A., May 1985. Sponsor: Bone Marrow Transplantation Team, U.T.S.C.C.

11. Invited speaker at the Canadian Red Cross Society, Toronto, Ontario, Canada, November 1985. Sponsor: Canadian Red Cross Society.

12. 32nd Annual Meetings of the Orthopedic Research Society, New Orleans, Louisiana, U.S.A. February 1986. (Poster)

13. European Molecular Biology and Biotechnology Summer Workshop. University of Paris VII, Paris, France, June-July 1987. (Oral Presentation)

14. Canadian Physiology Society Meeting, Mont Tremblant, Quebec, Canada, January 1988. (Poster)

15. 19th International Leukocyte Culture Conference, Banff, Alberta, Canada, May 1988. (Poster)

16. Canadian Society for Immunology - Spring Meeting, Lake Louise, Alberta, Canada, March 1989. (Poster)

17. Federation of American Societies for Experimental Biology Meeting, New Orleans, Louisiana, U.S.A., March 1989. (Poster)

18. Invited speaker at The University of Arizona, Health Sciences Centre, Tucson, Arizona, U.S.A., August 1989. Sponsor: NIH Alcohol Program, Department of Internal Medicine.

19. Invited speaker at The University of Nebraska Medical Centre, Omaha, Nebraska, U.S.A., September 1989. Sponsor: Department of Pathology and Microbiology, University of Nebraska.

20. European Federation of Immunological Societies Meetings, Edinburgh, Scotland, September 1990. (Oral Presentation)

21. Transplantation Immunology Summer School, British Transplantation Society and British Society for Immunology, Aberdeen, Scotland, September 1990. (Oral Presentation)

22. First International Congress on Xenotransplantation, Minneapolis, Minnesota, U.S.A., August 1991. (Oral Presentation)

23. Invited speaker at the N.A.T.O. Advanced Research Workshop on "Advances in Bacterial Paracrystalline Surface Layers", London, Ontario, Canada, September 1992.

24. Emerging Principles for Vaccine Development, Keystone Symposium, Taos, New Mexico, U.S.A., February 1993. (Poster)

25. Invited lecturer for Microbiology 410: Structure of Microorganisms, Department of Microbiology, University of Alberta, Edmonton, Alberta, Canada, March 1993.

26. University of Alberta - University of Calgary Conference on Infectious Diseases, Kananaskis, Alberta, Canada, May 1994 (Poster).

27. XVII International Carbohydrate Symposium, Ottawa, Ontario, Canada, July 1994 (Poster).

28. 10th Spring Meeting of the Canadian Society for Immunology - Spring Meeting, Lake Louise, Alberta, Canada, March 1995 (Poster).

29. 9th International Congress of Immunology, San Francisco, California, U.S.A., July 1995 (Poster).

30. XIII International Symposium on Glycoconjugates, Seattle, WA, U.S.A., August 1995 (Poster).

31. Third International Congress for Xenotransplantation, Boston, MA, U.S.A., September 1995 (Poster).

32. 7th International Congress of Infectious Diseases, Hong Kong, June 1996 (Poster).

33. 11th Spring Meeting of the Canadian Society for Immunology, Lake Louise, Alberta, Canada, March 1997 (Poster).

34. Annual Meeting of the Royal College of Physicians and Surgeons of Canada, Annual Meeting of the Canadian Transplantation Society, Vancouver, B.C.,Canada, September 1997 (Poster)

35. Invited speaker at Health Sciences Animal Welfare committee "Symposia on Xenotransplantation", University of Alberta, Edmonton, Alberta, October 1997.

36. International Conference on Xenotransplantation, Boston, MA, U.S.A., December 1997 (Poster).

37. 51st Annual Meeting of the Canadian Cardiovascular Society, Ottawa, Ontario, Canada, October 1998 (Poster).

38. 6th International Congress of Therapeutic Drug Monitoring and Clinical Toxicology, Cairns, Queensland, Australia, September 1999 (Oral Presentation and Posters)

PUBLICATIONS

M.Sc. Thesis: *The Effect of Hapten-Specific Suppression of IgE Production on Antigen Induced Histamine Release from Mouse Peritoneal Mast Cells.*
Supervisor: Dr. A.H. Sehon, Professor.

Ph.D. Thesis: *The Analysis of Human Myelogenous Leukemia Cells in the Fluorescence-Activated Cell Sorter.*
Supervisor: Dr. J.G. Levy, Professor.

JOURNAL PUBLICATIONS

1. Malcolm, A.J., Holford-Strevens, V. and Sehon, A.H. *The effect of hapten-specific suppression of IgE on antigen-induced histamine release from mouse peritoneal mast cells.* Int. Arch. Allergy Appl. Immunol. 59 286-297, 1979.

2. Ramsey, E.W., Malcolm, A.J. *The leukocyte adherence inhibition assay as a measure of anti-tumor immunity in bladder cancer patients.* J. Urology 126: 600-603, 1981.

3. Al-Rammahy, A.K., Shipman, R., Jackson, A., Malcolm, A.J. and Levy, J.G. *Evidence of a common leukemia associated antigen in acute myelogenous leukemia.* Cancer Immunol. Immunother. 96: 858-866, 1980.

4. Malcolm, A.J., Shipman, R.C., and Levy, J.G. *Detection of a tumor-associated antigen on the surface of human myelogenous leukemia cells.* J. Immunol. 128: 2599-2603, 1982.

5. Malcolm, A.J., Logan, P.M., Shipman, R. and Levy, J.G. *Analysis of human myelogenous leukemia cells in the fluorescence-activated cell sorter using a tumor-specific antiserum.* Blood 61: 858-866, 1983.

6. Shipman, R., Malcolm, A.J. and Levy, J.G. *Partial characterization of a membrane antigen which demonstrates specificity for cells of patients with acute myelogenous leukemia.* Br. J. Cancer 47: 849-852, 1983.

7. Malcolm, A.J., Shipman,R.C., Logan, P.M. and Levy, J.G. *A monoclonal antibody to myelogenous leukemia: Isolation and characterization.* Exper. Haematology 12: 539-547, 1984.

8. Logan, P.M., Malcolm, A.J. and Levy, J.G. *Immunoperoxidase studies using a monoclonal antibody provide evidence for increased expression of a common leukemia-associated antigen in human myelogenous leukemia.* Diag. Immunol. 2: 86-97, 1984.

9. Levy, J.G., Logan, P.M., Whitney, S., Malcolm, A.J., Naiman, S., Powles, R. and Crawford,D. *Demonstration of a leukemia-associated antigen (CAMAL) in peripheral blood leukocytes of bone marrow transplant patients prior to relapse.* Transplantation 40: 167-173, 1985.

10. Cruz, T.S., Malcolm,A.J. and Adams, M.E. *The effect of maturation and anterior cruciate ligament transection on the level of keratin sulfate in the serum of dogs.* J. Rheumatology 16: 1345-1350, 1989.

11. Caterson, B., Calabro, T., Adams,M. and Malcolm, A. *Methods for production and characterization of monoclonal antibodies against connective-tissue proteoglycans.* In "Methods in cartilage research" ed. A. Maroudas and K. Kuettner, Academic Press, New York, Chapter 41: 164 - 167, 1990.

12. Leranth, C., Malcolm, A.J. and Frotscher, M. *Afferent and efferent synaptic connections of somatostatin - immunoreactive neurons in the rat fascia dentata.* J.Comp. Neurol. 295: 111-122, 1990.

13. McIntosh, C.H.S., Tang, C.L., Malcolm, A.J., Ho, M., Kwok, Y.N., and Brown, J.C. *Effect of a purified somatostatin monoclonal antibody and its fab fragments on gastrin release.* Am. J. Physiol. 260: G489-489, 1991.

14. Malcolm, A.J., Ho, M. and Brown J.C. *Isolation and purification of gastric inhibitory polypeptide with a specific monoclonal antibody.* Submitted to Regulatory Peptides

15. Malcolm, A.J. and Brown, J.C. *Evidence that the non-opioid portion of gamma endorphin enhances human cytolytic responses.* Submitted to J. Immunol.

16. Malcolm, A.J., Ho, M. and Brown, J.C. *Enhancement of lymphocyte cytotoxic responses and tumor rejection by opioid peptides in a mouse model.* Submitted to Immunol. Letters.

17. Good, A. H., Cooper, D. K. C., Malcolm, A. J., Ippolito, R. M., Koren, E., Neethling, F. A., Ye, Y., Zuhdi, N. and Lamontagne, L. R. *Identification of carbohydrate structures which bind human anti-porcine antibodies: Implications for xenografting in humans.* Transplantation Proceedings 24: 559 - 562, 1992.

18. Malcolm, A.J., Messner, P., Sleytr, U.B., Smith, R.H., and Unger, F.M. *Crystalline bacterial cell surface layers (S-Layers) as combined carrier/adjuvants for conjugate vaccines.* In "Immobilised macromolecules: Application potentials" eds. U. B. Sleytr, P. Messner, D. Pum and M. Sàra, Springer-Verlag, London, Chapter 13: 195 - 207, 1993.

19. Malcolm, A. J., Best, M. W., Szarka, R. J., Mosleh, Z., Messner, P., Sleytr, U. B., and Unger, F. M. *Surface layers from Bacillus alvei as a carrier for a Streptococococcus pneumoniae conjugate vaccine.* In "Advances in bacterial paracrystalline surface layers", eds. T. J. Beveridge and S. F. Koval, Plenum Press, New York, Chapter 21: 219 - 233, 1993.

20. Cooper, D.K., Good, A. H., Koren, E., Oriol, R., Malcolm, A. J., Neethling, F. A., Romano, E. and Zuhdi, N. *Specific intravenous carbohydrate therapy; a new approach to the inhibition of antibody-mediated rejection following ABO-incompatible allografting and discordant xenografting.* Transplantation Proceedings 25: 377- 378, 1993.

21. Cooper, D. K. C., Good, A. H., Koren, E., Oriol, R., Malcolm, A. J., Ippolito, R. M., Neethling, F. A., Ye, Y., Romano, E. and Zuhdi, N. Identification of I-galactosyl and other carbohydrate epitopes that are bound by human anti-pig antibodies: Relevance to discordant xenografting in man. Transplant Immunology 1: 198 - 205,1993.

22. Aspeslet, L., Malcolm, A. J., Mosleh, Z., Koshal, A. and Yatscoff, R.W. Identification of porcine membrane antigens involved in the cytotoxic response to human xenoantibodies. Xenotransplantation 3: 1-10, 1996.

23. Korbutt, G.S., Aspeslet, L., Warnock, G. L., Ao, Z., Ezekowitz, J., Malcolm, A. J., Koshal, A., and Yatscofff, R. W. Natural human antibody-mediated destruction of porcine neonatal islet cell grafts. Xenotransplantation 3: 207 - 216, 1996.

24. Malcolm, A.J. Novel glyco-conjugate bacterial vaccines. European Pharmaceutical Contractor 48-52, Feb, 1999.

25. Fryer, J., Firca, J., Leventhal, J., Blondin, B., Malcolm, A., Ivancic, D., Ghandi, R., Shah, A., Pao, W., Abecassis, M., Kaufman, D., Stuart, F., and Anderson, B. IgY anti-porcine endothelial cell antibodies effectively block human anti-porcine xenoantibody binding. Xenotransplantation 6(2): 98-109, 1999.

26. Malcolm, A. J. and Mosleh, Z. Multi-hapten conjugate vaccines (Manuscript in preparation).

27. Malcolm, A. J., Thomas, T., Mendez, R. and Mosleh, Z. Identification of non-galactosyl moieties relevant to xenograft rejection. (Manuscript in preparation).

28. Latham, T., Malcolm, A., Thomas, T., Mosleh, Z., Koshal, A. and Yatscoff, R. Removal and suppression of xenoantibodies in cynomolgus monkeys. (Manuscript in preparation).

29. Malcolm, A. J.,Naicker, S. and Yatscoff, R. Therapeutic drug monitoring assays utilizing monoclonal antibodies derived to cyclosporin metabolite conjugates. (Manuscript in preparation).

ALLOWED, ISSUED AND PENDING PATENT APPLICATIONS

1. **"Methods and Compositions for Attenuating Antibody-Mediated Xenograft Rejection in Human Recipients"** – Xenograft Anti-Rejection Technology
   Inventors: A. Heather Good, David K.C. Cooper and Andrew J. Malcolm.
   U.S. application filing date - August 1992
   - Issued U.S. patent no. 5,651,968 – July 29, 1997
   - Issued U.S. patent no. 5,695,759 – Dec. 9, 1997
   - Issued U.S. patent no. 5,767,093 – June 16, 1998
   - Issued U.S. patent no. 5,977,079 – Nov 2,1999

   International PCT publication no. WO93/03735 – March 4, 1993
   (countries elected: Australia, Canada, EPO, Israel and Japan)
   - Issued Australian patent no. 666,128 – Feb. 1,1996

2. **"Immunogenic Oligosaccharide Compositions"** - Vaccine Development
   Inventor: Andrew J. Malcolm.
   U.S. application filing date - June 1995
   Canadian application filing date - July 1995
   - Issued U.S. patent no. 5,807,553 – Sept. 15, 1998
   - Issued U.S. patent no. 5,866,132 – May 1, 1999

3. **"Immunostimulating Activity of *Streptococcus Pneumoniae* Serotype 8 Oligosaccharides"** -Adjuvant Development.
   Inventor: Andrew J. Malcolm.
   U.S. application filing date - June 1995
   Canadian application filing date - July 1995
   - Issued U.S. patent no. 5,695,768 – Dec. 9,1997
   - Issued U.S. patent no. 5,855,901 – Jan. 5, 1999
   - Issued U.S. parent no. 5,916,571 – Jun. 29,1999

4. **"Immunogenic and Immunostimulating Oligosaccharide Compositions"** - Vaccine Development.
   Inventor: Andrew J. Malcolm
   PCT filing date - June 1996
   International PCT publication no. WO96/40225 – Dec. 19, 1996
   (countries elected: Australia, Czech Republic, EPO, Finland, Israel, Japan, Mexico,

South Korea, New Zealand and Norway)

5. **"A Method for Production of Antibodies to Sp cific Sites of Rapamycin"** – Therapeutic Drug Monitoring
   Inventors: Randall W. Yatscoff, Andrew J. Malcolm and Selvaraj Naicker
   PCT filing date - April 9, 1998
   U.S. application filing date – July 7, 1998

6. **"A Method for Production of Antibodies to Specific Sites of Cyclosporin and Cyclosporin Metabolites"** – Therapeutic Drug Monitoring.
   Inventors: Randall W. Yatscoff, Andrew J. Malcolm and Selvaraj Naicker
   U.S. application filing date – October 9, 1998
   PCT filling- September 3, 1999